IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
(Alexandria Division)

AVANIR PHARMACEUTICALS, INC., and CENTER FOR NEUROLOGIC STUDY,

Plaintiffs,

v.

DAVID KAPPOS, in his official capacity as Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office; and UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendants.

Civil Action No. 1:12cv69 GBL/TRJ

COMPLAINT

Plaintiffs Avanir Pharmaceuticals, Inc. ("Avanir") and Center for Neurologic Study ("CNS"), for their Complaint against defendants David Kappos and United States Patent and Trademark Office ("PTO"), allege as follows:

Nature of the Action

1. This is a civil action under the Administrative Procedure Act, 5 U.S.C. §§551-706, seeking to set aside the denial of an application—pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (commonly known as the "Hatch-Waxman Act")—to extend the term of a pharmaceutical patent exclusively licensed to Avanir. A copy of the patent at issue—United States Patent No. 5,206,248 (the "'248 patent")—is attached hereto as Exhibit 1.

2. Under 35 U.S.C. § 156 of the Hatch-Waxman Act, the holder of a drug patent, or its agent, is entitled to apply for a patent term extension ("PTE") to compensate for the delay in obtaining Food and Drug Administration ("FDA") approval to market or use a drug covered by the patent. In this action, Avanir challenges the denial of its application to extend the term of a patent covering its drug Nuedexta®.

3. Nuedexta® is the first and only treatment approved by the FDA for pseudobulbar affect ("PBA"), a neurological condition characterized by involuntary episodes of laughing and/or crying in patients with underlying neurological disease or injury. Nuedexta® contains, among other ingredients, dextromethorphan hydrobromide and quinidine sulfate. Taken by themselves dextromethorphan is a cough suppressant and quinidine treats heart arrhythmias and neither dextromethorphan nor quinidine alone has any effect on PBA. However, together in Nuedexta®, the dextromethorphan/quinidine is a wholly new active ingredient that treats PBA. The '248 patent covers this use of dextromethorphan/quinidine.

4. Based on the 12-year FDA regulatory review of Nuedexta®, Avanir filed an application for the extension of the term of the '248 patent under 35 U.S.C. § 156 with the PTO.

5. On December 20, 2011, the PTO denied Avanir's request for patent term extension. That denial was erroneous, and arbitrary and capricious, for at least two reasons.

6. First, the PTO erroneously defined the relevant "product" for purposes of 35 U.S.C. § 156 as either dextromethorphan alone or quinidine alone, both of which had individually received prior FDA approval, rather than as dextromethorphan/quinidine. It is undisputed, however, that neither dextromethorphan nor quinidine are able to treat PBA by themselves. In fact, it is clear that the single ingredient responsible for Nuedexta®'s

therapeutic effect is not dextromethorphan or quinidine, but dextromethorphan/quinidine. There is also no dispute that Nuedexta® represents the first time that dextromethorphan/quinidine has been approved by the FDA. Nevertheless, the PTO arbitrarily and capriciously ignored these facts, focused only on whether dextromethorphan and quinidine had been approved individually, and denied Avanir's request for a PTE.

7. Second, the PTO erroneously determined that dextromethorphan has previously been the subject of a "regulatory review period" under the same "provision of law" under which Nuedexta® was approved. This conclusion is misplaced because, as explained above, the active ingredient in Nuedexta® is dextromethorphan/quinidine, not dextromethorphan alone. The PTO's denial of Avanir's PTE request is erroneous, arbitrary and capricious for this reason alone. But even if dextromethorphan alone is considered the active ingredient in Nuedexta®, the PTO's denial of Avanir's PTE request is still arbitrary and capricious. Indeed, it is undisputed that Nuedexta® was approved for commercial marketing under the version of § 505 of the Federal Food Drug and Cosmetic Act ("FFDCA") in effect on October 29, 2010, which requires proof of efficacy as well as safety. It took Avanir more than 12 years to complete regulatory review of Nuedexta®. It is also undisputed that all other dextromethorphan products were approved by FDA under the pre-1962 version of § 505 of the FFDCA, which required no proof of efficacy, and no "regulatory review period." Despite these undisputed facts, FDA arbitrarily and capriciously found that the pre-1962 dextromethorphan products have been the subject of a "regulatory review period" and denied Avanir's request for a PTE.

8. The PTO's decision is not merely arbitrary and capricious; it is profoundly unfair and undermines the remedial design of the patent term restoration system. The decision

furthers no statutory purpose yet threatens to inflict enormous harm on Avanir. Avanir spent more than 12 years and over 200 million dollars to develop Nuedexta®, and sales of Nuedexta® account for substantially all of Avanir's revenue. Furthermore, by erecting an arbitrary barrier to obtaining patent term extensions, the PTO's position would erode the Hatch-Waxman Act's incentives designed to encourage the expensive, time-consuming, and risky research and development necessary to bring a new drug product to market.

9. Neither the statute, the regulations, nor common sense mandates such a result. The process of developing, testing, and obtaining regulatory approval for the use of Nuedexta® took more than a decade and consumed at least 12 years of Avanir's patent term. Recognizing that this type of regulatory delay substantially diminishes the effective life of a patent, Congress enacted remedial legislation specifically mandating that patent terms be restored to compensate companies for the economic value lost during the review period, thereby preserving the incentive to create, develop, and secure regulatory approval for innovative new drugs.

10. For the reasons set forth herein, the PTO's decision to deny Avanir's application should be set aside and the matter remanded to the PTO.

The Parties

11. Plaintiff Avanir Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 20 Enterprise, Suite 200, Aliso Viejo, California 92656.

12. Plaintiff Center for Neurologic Study is a not-for-profit corporation organized and existing under the laws of the State of California, having a principal place of business at 9850 Genese Avenue, Suite 320, La Jolla, California 92037.

13. Defendant David Kappos is the Under Secretary of Commerce for Intellectual Property and Director of the PTO. Mr. Kappos is sued in his official capacity as Director.

14. Defendant PTO is a federal agency within the Department of Commerce that is headquartered in Alexandria, Virginia.

Jurisdiction and Venue

15. This Court has jurisdiction over this action—which arises under 5 U.S.C. §§ 702 & 704, 28 U.S.C. § 2201, and 35 U.S.C. § 156—pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1361.

16. There exists between the parties an actual, justiciable controversy as to which Avanir requires a declaration of its rights by the Court.

17. Venue is proper in this Court pursuant to 28 U.S.C. § 1391(e)(l) because Defendants Kappos and PTO reside in the Eastern District of Virginia.

18. Venue is proper in this Division pursuant to Local Civ. R. 3(C) because Defendants Kappos and PTO reside in the Alexandria Division.

Statutory Framework

19. A new drug cannot be commercially marketed or used until the FDA approves it under § 505 of the FFDCA, 21 U.S.C. § 355(a).

20. Before the 1962 Drug Amendments to the FFDCA, New Drug Applications ("NDA") only had to include safety data. FFDCA, ch. 675, sec. 505, 52 STAT. 1040, 1052 (1938). The FDA neither "reviewed" nor "approved" these NDAs before the products could be marketed. Instead, by operation of the statute, NDAs became automatically effective 60 days after they were filed, unless the FDA determined that it needed more time to "study and investigate the application." *Id.* at § 505(c) (1938). Even in the instances where the FDA determined that "study and investigate" was appropriate, however, upon completing such study

and investigation, the FDA could only prevent an application from becoming effective in limited circumstances: if the sponsor failed to demonstrate that the drug was safe; or if the sponsor could not demonstrate that it had adequate control over its manufacturing process. *Id.* at § 505(d) (1938). There was no requirement of proving efficacy, and, significantly, the words "review" and "approval" do not appear in the relevant portions of § 505 as it existed before 1962.

21. In 1962, Congress amended the FFDCA to require that all new drugs must be proven effective, as well as safe, before coming to market. *See* FFDCA, Drug Amendments of 1962, Pub. L. No. 87-781, § 505, 76 STAT. 781 (1962). This radical transformation in the requirements for NDA approval demanded that efficacy be shown by controlled tests—that is, by studies where some diseased persons receive the drug in question while other diseased persons, otherwise comparable, receive nothing, or a "placebo," or some substance of known effect. Generally, the 1962 Amendments required—for the first time—that:

1. NDAs must contain both safety and effectiveness data (*See* 21 U.S.C. § 355(a));

2. NDAs do not become automatically effective by operation of law after a specified period of time (*See id* at § 355(b)); and

3. After a detailed substantive review of an NDA, the agency has the affirmative duty to determine if the NDA is approvable (*See id* at § 355(c)).

22. In the present era, the twin concepts of review and approval are inseparably linked to NDA submissions. For this and other reasons, the process of securing FDA approval for a new drug is extraordinarily time consuming and expensive. A new drug applicant must conduct clinical studies and submit detailed information to the FDA regarding both safety and efficacy. *Id.* § 355(b)(l); 21 C.F.R. § 314.50. During this process, the applicant receives no commercial benefit from any patents on the drug.

23. Concerned that this shortening of the effective patent term was diminishing the incentive to create and develop innovative new drug products, Congress enacted Title II of the Hatch-Waxman Act, which is codified in relevant part at 35 U.S.C. § 156. Under § 156, the holder of a drug patent or its agent is entitled to apply for a patent term extension to "compensate for the delay in obtaining FDA approval." *Merck & Co. v. Kessler*, 80 F.3d 1543, 1547 (Fed. Cir. 1996). The Act is thus remedial, and its ultimate purpose is to "encourage[] drug manufacturers to assume the increased costs of research and development of certain products which are subject to premarketing clearance." H.R. Rep. No. 98-857, pt. II, at 11 (1984), reprinted in 1984 U.S.C.C.A.N. 2686, 2695.

24. In order to seek a patent term extension, the patent holder or its agent must file a detailed application with the PTO. *See id.* at § 156(d)(l). Such an application must contain, among other things, "the identity of the patent for which an extension is being sought and the identity of each claim of such patent which claims the approved product or method of using or manufacturing the approved product"; "information to enable the Director [of the PTO] to determine . . . the eligibility of [the] patent for an extension"; detailed "information to enable [determination of] . . . the period of the extension"; and a "brief description of the activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities." *Id.*; *see also* 37 C.F.R. § 1.740.

25. Under 35 U.S.C. § 156(a)(5)(A), one of the requirements for patent term extension is that the drug approval is the "the first permitted commercial marketing or use of the product." The term "product" is further defined by § 156(f) as follows:

> (f) For purposes of this section:
> (1) The term "product" means:

> (A) A drug product. …
> (2) The term "drug product" means the active ingredient of--
> (A) a new drug …
> including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.

26. Another requirement of 35 U.S.C. § 156(a)(5)(A) is that the patented drug has undergone a "regulatory review period" prior to approval, but only for the "first permitted commercial marketing" of the drug "under the provision of law under which the regulatory review period occurred."

The Development of Nuedexta®

27. Nuedexta® is a novel drug product comprising dextromethorphan hydrobromide and quinidine sulfate. Nuedexta® was the first commercial drug product containing the combination dextromethorphan/quinidine; prior to its approval, those components had only been available separately, for uses unrelated to PBA. Nuedexta® was thus deemed a new drug, as defined under § 201(p) of the FFDCA, and, accordingly, a New Drug Application ("NDA") approved by the FDA was required before the product could be commercially marketed.

28. Dextromethorphan has previously been used as a cough-suppressant (antitussive) agent and has been investigated for other conditions based on its pharmacological properties. Dextromethorphan is a sigma-1 receptor agonist and a weak, uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. Glutamate, an NMDA receptor agonist, is the primary excitatory neurotransmitter in the mammalian central nervous system ("CNS"), with up to 70% of excitatory CNS synapses utilizing glutamate as a transmitter.

29. Because of the potential for neuroprotective effects by NMDA receptor antagonists, oral administration of dextromethorphan (in many cases at doses greater than the maximum recommended antitussive dose of 120 mg/day) has been investigated as a treatment for neurodegenerative diseases including ALS, Huntington's disease, Parkinson's disease, and

stroke. Dextromethorphan, however, has been ineffective in treating these diseases because it is rapidly metabolized before it can cross the blood-brain barrier. Specifically, dextromethorphan is extensively metabolized by a liver enzyme known as cytochrome P450 2D6 ("CYP2D6.")

30. Quinidine is an antiarrhythmic drug at very high doses. At doses that are much lower than the recommended antiarrhythmic dose, Dr. Richard A. Smith, the listed inventor on the '248 patent, discovered that quinidine effectively inhibits the metabolism of dextromethorphan by CYP2D6. Quinidine, therefore, allows dextromethorphan to cross the blood-brain barrier. Dr. Smith's studies demonstrated that when dextromethorphan was administered with quinidine, patients reported a palliative effect on PBA.

31. Thereafter, Avanir filed an Investigational New Drug ("IND") Application with the FDA for Nuedexta®, which became effective on October 21, 1998. Avanir subsequently had to conduct numerous time-consuming, expensive clinical studies in connection with gaining FDA approval for Nuedexta®. Indeed, as the FDA noted during its regulatory review of Nuedexta®, dextromethorphan had only previously been considered by the FDA as an antitussive, and then only at blood plasma levels far lower than those that would be achieved by Nuedexta®:

> Dextromethorphan is currently approved for short-term use (e.g., temporary relief of cough due to colds), whereas [Nuedexta®] is intended for chronic administration. In addition, plasma levels of dextromethorphan are increased up to 40-fold following administration of [Nuedexta®] compared to dextromethorphan alone. . . . it is clear that systemic exposure to dextromethorphan will substantially exceed the exposure for which there is previous human experience, at least in patients who are CYP2D6 extensive metabolizers (EMs).

32. The clinical studies conducted by Avanir demonstrated that neither dextromethorphan nor quinidine could effectively treat PBA by themselves. They also

demonstrated that dextromethorphan/quinidine had properties wholly different than either drug alone, and that the dextromethorphan/quinidine combination is significantly more effective in treating PBA than placebo or either of the individual components. Based on these studies, the FDA approved Avanir's Nuedexta® NDA on October 29, 2010. In total, Avanir spent more than 12 years and $200 million in getting Nuedexta® through the FDA approval process.

The PTO's Denial of Patent Term Extension

33. On December 17, 2010, Avanir requested extension of the patent term of the '248 patent based on the 12-year regulatory review period of Nuedexta®. On December 20, 2011, the PTO issued a Final Determination of Ineligibility for an extension of the patent term of the '248 patent under 35 U.S.C. § 156. The PTO's Final Determination is attached hereto as Exhibit 2. In making that determination, the PTO found that although Nuedexta® met the first four requirements of 35 U.S.C. § 156(a), it did not meet § 156(a)(5) because Nuedexta® was allegedly not the first commercial marketing of the product. That decision was erroneous and arbitrary and capricious.

Count I: Administrative Procedure Act

34. Plaintiffs incorporate the preceding paragraphs as if fully set forth herein.

35. The PTO's denial of Avanir's application for a patent term extension failed to provide adequate explanations for the PTO's conclusions, failed to respond to significant arguments raised by Avanir, reflected a misapprehension of agency authority under § 156, and misinterpreted federal statutes, agency regulations, and relevant case law.

36. Accordingly, these decisions were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law" pursuant to 5 U.S.C. § 706(2)(A).

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court:

(A) Vacate and set aside the PTO's December 20, 2011 decision denying Avanir's application for an extension of the term of U.S. Patent No. 5,206,248;

(B) Order the PTO to extend the term of U.S. Patent No. 5,206,248 for the full period required under 35 U.S.C. § 156;

(C) Expedite consideration of this case and grant any preliminary injunctive relief necessary to maintain the status quo pending resolution of this case;

(D) Award Avanir its costs and reasonable attorney's fees as appropriate; and

(E) Grant such further and other relief as this Court deems just and proper.

Dated: January 23, 2012

Respectfully submitted,

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